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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/623,442	07/18/2003	Tae-Wan Kim	66195/JPW/AJM/JCS	3560

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/623,442	KIM ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *6-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/24/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-22 are pending.

2. Applicant's election with traverse of Group I, claims 1-5 and 20-22 drawn to an isolated CD44 fragment and an article of manufacture filed on 4/3/06, is acknowledged.

Applicant's traversal is on the grounds that there would not be a serious burden on the Examiner if restriction were not required, because a search of the prior art relevant to the claims of Group I would provide the relevant prior art for Groups II-XIII. Applicant contents that the compositions and methods of Groups XII-XIII employ the CD44 fragment of Group I. Accordingly, Applicant concludes that there is no burden on the Examiner to examine Groups I-XIII together in the same application. This is not found persuasive because the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the isolated CD44 fragment of Group I can be used for affinity purification, in addition to the methods recited in Groups XII and XIII. Therefore the methods of Groups I, XII and XIII are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 6-19 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-5 and 20-22 are under examination as they read on an isolated CD44 fragment and an article of manufacture.

5. Applicant's IDS, filed 10/24/03, is acknowledged.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-5 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide **enablement** for an isolated CD44 fragment, which fragment comprises the amino acid sequence of a fragment formed in a $CD44^+$ cell in the presence of extracellular hyaluronan and of intracellular γ-secretase and metalloprotease in claim 1, wherein the fragment formed in the $CD44^+$ cell in a cleavage product of γ-secretase in claim 2 or a polypeptide comprising the CD44 fragment of claim 1, wherein at least on amino acid residure thereof is an amino acid derivative in claim 3, or a compostion comprising the CD44 fragment of claim 1 and a pharmaceutically acceptable carrier in claim 4, wherein the carrier is a 16 amino acid polypeptide of the Antennapedia protein of the Drosophila fruit fly in claim 5, or an article of manufacture comprising a packaging material having therein the CD44 fragment of claim1, and a lable indicating a sue for the CD44 fragment in treating a CD44-associated disorder in claim 20, wherein the CD44-associated disorder is cancer in claim 21 or streptococcal invasion in claim 22. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

The specification fails to disclose any particular function or biological significance for the CD44ICD polypeptide. The disclosed CD44 fragment is said to have a potential function based upon γ-secretase-mediated cleavage of CD44 is associated with the observed growth inhibition induced by HA (see page 17, lines 10-14). Further, that CD44 undergoes presenilin-dependent intramembrane proteolysis may be critical for regulating cell growth and other CD44-mediated cellular processes (see page 18 lines 1-12). The examiner notes that it is not the CD44ICD that is associated with the observed growth inhibition induced by HA, but rather the soluble CD44 fragment. Further, the Examiner notes that the CD44ICD fragment which is released by sequential proteolytic cleavages translocates into the nucleus (see Okamoto et al (2001), page 758, 1st col.,) and acts as transcriptional factor (see Okamoto et al (2001), page 758, 2nd col.,). Finally, it is noted that the specification used the γ-secretase inhibitor i.e., Compound E, but not CD44ICD fragment to show the importance of CD44ICD in growth inhibition induced by HA. After further research, specific and substantial function or biological significance might be found for the claimed purified CD44 fragment. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

At issue is whether or not the claimed article of manufacture would function to treat a CD-44-associated disorder including cancer and streptococcal. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the article of manufacture as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed article of manufacture are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed article of manufacture with a reasonable expectation of success.

The lack of any working examples is exacerbated because the invention is in a highly unpredictable art-CD44 associated disorder- and while the level of skill of in the art may be high, the state of the prior art is that it is in fact unknown and untested what are the underlying cell growth molecule and physiologic bases of the therapeutic effects of CD44ICD in the treatment of CD-44-associated disorder.

On the basis of the disclosed correlation of the γ-secretase-mediated cleavage of CD44 and the tendency of inhibition of cell growth induced by HA observation alone (see specification on page 17, lines 1-15), applicant concludes that the scope of the claimed CD44 fragment encompassed by the claimed invention can have biological activity to treat CD44-associated disorder such as cancer and streptococcal and be provided as pharmaceutical compositions to subjects including human to effectively treat cancer or streptococcal. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Further at issue is the amino acid derivative claimed in claim 3. Applicant has not provided sufficient biochemical information that distinctly identifies such "derivatives". While any CD44 fragments may have some notion of the activity, claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such polypeptide, commensurate in scope with the claimed invention. The specification fails to provide any guidance on how to make polypeptide comprising the CD44 fragment that can be used to treat CD44 mediated disorders.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by Okamoto *et al* (JCR, 155(5):755-762, Nov. 2001).

Okamoto *et al* teach an isolated CD44 fragment, CD44ICD, which fragments comprise the amino acid sequence of a fragment formed in a $CD44^+$ cell (U251MG cells) in the presence of intracellular γ-secretase (γ -secreatase-mediated) and metalloprotease (metalloprotease mediated). In particular, Okamoto *et al* identified three peptides matching, covering 80% of CD44 intracellular domain (see Fig. 1A-C in particular). Okamoto *et al* teaches a peptide composed of amino acid residues 288-324 of CD44 (CD44ICD) (see page 756, last ¶ in

particular). CD44ICD is a cleavage product of γ-secretase because MG132 (block γ-secretase-mediated intracellular proteolytic cleavages) treated cells produce only CD44 ectodomain cleavage product but no CD44ICD fragment (see page 756, last ¶ and Figure 2A lines 1 and 5in particular). Finally, Okamoto *et al* teach the CD44ICD proteolytic fragment dialyzed against 0.01 X PBS, which is considered to be a pharmaceutically acceptable carrier.

Claim 3 is included because Okamoto et al teaches a polypeptide comprises CD44ICD and HA/Myc/fluorescent tag (see page 758, the paragraph bridging col., 1 and col., 2 in particular). The tag is considered to be an amino acid derivative.

While the prior art is silent with respect to the presence of extracellular hyaluronan (HA), the reference teaches the use of TPA which has similar effects as HA. Further, the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985), MPEP 2113.

The reference teachings anticipate the claimed invention.

10. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Okamoto *et al* (JBC, 274(36):25525-25534, 1999) as is evidence by Okamoto *et al* (JCR, 155(5):755-762, Nov. 2001).

Okamoto *et al* (1999) teach a CD44 cleavage product through intracellular proteolytic pathways, and occurs only after CD44 extracellular cleavage (see abstract). Okamoto *et al* (1999) further teach that the CD44 cleavage product was hardly detectable when the U251MG cells ($CD44^+$ cells) were directly lysed with SDS sample buffer without scraping. However, when the lysate were prepared from the proteosome inhibitor MG132-treated U251MG cells without mechanical scraping, three bands of with apparent molecular masses between 20-30 kDa became apparent. The bands were absent in the presence of the metalloprotease inhibitor BB2516, indicating that these fragments are generated by metalloprotease-mediated CD44 cleavage at the extracellular domain. Further, The difference in the size of the three fragments suggests existence of plural cleavage sites in the membrane proximal of CD44 ectodomain or modifications of the CD44 cleavage product (see Fig. 1 and page 25527, 1st col., 1st ¶ in particular). While Okamoto *et al* (1999) reference teachings is silent with respect to γ-secretase, the 20 kDa fragment is the product of γ-secretase proteolytic cleavage as is evidenced by Okamoto *et al* (2001) that the CD44 ectodmain fragment is further cleaved to 20 kDa with γ-secretase in the absence of the γ-secretase inhibitor (see Fig. 2 and page 756, 2nd col., last ¶ in particular).

While the prior art is silent with respect to the presence of extracellular hyaluronan (HA), the reference teaches the use of TPA which has similar effects as HA. Further, the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985), MPEP 2113.

The reference teachings anticipate the claimed invention.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claim 1, 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okamoto et al (1999) or Okamoto et al (2001) each in view of US. Pat. No. 5,968,824.

The teachings of Okamoto *et al* (1999 and 2001) references have been discussed, supra. Further, Okamoto *et al* (1999) teach that CD44ICD tagged with HA at its NH2 terminus. Also immunofluorescence staining of the transfected cells revealed that CD44ICD was localized to the nucleus (see page 758, 1st col., 1st full ¶ in particular).

The claimed invention differs from the reference teachings only by the recitation of a pharmaceutically acceptable carrier in claim 4, wherein the carrier is a 16 amino acid polypeptide of the antennapedia protein of the Drosophila fruit fly.

The `824 patent the expression "internalization peptide" relates to peptides which can facilitate transport of a molecule through a cell surface membrane. Examples of suitable internalization peptides are under the trade name "PENETRATIN". PENETRATIN® peptide is a 16 amino acid polypeptide of thye antennapedia protein of the Drosophila fruit fly as is evidenced by the specification on page 12, lines 1-3.

Given that the CD44ICD is localized to the nucleus or cytoplasmic domain of the $CD44^+$ cells, it would have been obvious to one of ordinary skill in the art at the time the invention was made to link the CD44 fragment taught by Okamoto et al (2001) or to substitute the HA tag of CD44ICD taught by Okamoto et al (1999) with PENETRATIN® peptide as taught by US. `824 Patent to facilitate transport of the CD44 fragment through a cell surface membrane as taught by `824 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claims 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okamoto et al (1999) or Okamoto et al (2001) each in view of US. Pat. No. 4,761,406.

The teachings of Okamoto *et al* (1999 and 2001) references have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of an article of manufacture comprising the CD44 fragment and a label in claim 20-22.

The `406 patent teach kits which facilitate the necessary strict compliance with methods of treatments (e.g., see column 1, paragraph 1; column 2, paragraph 3 and columns 13-15).

It would have been prima facie obvious to the ordinary artisan to include a piece of paper in the kit identifying the components therein at the time the invention was made.

With respect to the specific textual information on the piece of paper (i.e. instructions for the use of the CD44); the specific textual information does not convey patentability, since the printed matter on a label or package insert does not lend patentable weight as a limitation of the claimed product. Also, see In re Haller 73 USPQ 403 (CCPA 1947) and In re Venezia 189 USPQ 49 (CCPA 1976).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the CD44 fragment taught by Okamoto et al (1999 and 2001) and a piece of paper in a kit to facilitate the necessary strict compliance with methods of treatments as taught by the `406 Patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 8, 2006

Maher Haddad

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